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Cost-effectiveness of combination disease-modifying antirheumatics vs. tumour necrosis factor inhibitors in active rheumatoid arthritis: TACIT trial

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Competing interests

The authors declare that they have no competing interests.

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ABSTRACT

Objective

To determine whether intensive combinations of synthetic disease modifying drugs (cDMARDS) achieve similar clinical benefits more cheaply than high-cost biologics such as tumour necrosis factor inhibitors (TNFis) in patients with active rheumatoid arthritis (RA) who have failed to respond to methotrexate and another DMARD.

Methods

Within-trial, cost-effectiveness and cost-utility analyses from health and social care (H&SC) and two societal perspectives. Participants were recruited into an open-label, 12-month, pragmatic, randomised, multicentre, two-arm, non-inferiority trial in 24 rheumatology clinics in England. Costs were linked with the Heath Assessment Questionnaire (HAQ; primary outcome) and quality-adjusted life years (QALYs) derived from two measures (SF-36, EQ-5D-3L).

Results

205 participants were recruited, 104 in the cDMARDs arm, 101 in the TNFis arm. cDMARD arm participants with poor response at 6 months were offered TNFis; 46 (44%) switched. Relevant cost and outcome data were available for 93% of participants at 6 month follow-up and 91-92% at 12 month follow-up. The cDMARDs arm had significantly lower total costs from all perspectives (6 month H&SC adjusted mean difference -£3615 (95% confidence interval -£4104 to -£3182); 12 month H&SC adjusted mean difference -£1930 (95% confidence interval -£2599 to -£1301)). The HAQ showed benefit to the cDMARDs arm at 12 months (-0.16; 95% CI-0.32 to -0.01); other outcomes/follow-ups showed no differences.

Conclusion

Starting treatment with cDMARDs, rather than TNFis, achieves similar outcomes at significantly lower costs. Patients with active rheumatoid arthritis and meeting NICE criteria for expensive biologics can cost-effectively be treated with combinations of intensive synthetic disease modifying drugs.

KEY WORDS

Rheumatoid Arthritis; Economic evaluations; Anti-TNF; DMARDs.

SIGNIFICANCE AND INNOVATIONS

- Our results show that cDMARDs are a more cost-effective treatment approach for RA as the cDMARDs group achieved similar outcomes compared with the TNFi group at significantly lower costs. This is important in the context of ongoing cost-effectiveness and affordability concerns regarding the use of biologics.

- High quality cost-effectiveness evidence is vital to inform resource allocation decisions. These results are based on a robust, comprehensive and prospective trial-based economic evaluation in the context of an evidence base thus far dominated by modelling studies.

Rheumatoid arthritis (RA) is a common long-term inflammatory disorder affecting 0.5-1% adults in industrialised countries,[1] characterised by persisting joint inflammation. Consequences span erosive joint damage, systemic comorbidities like cardiovascular disease[2] with consequent reductions in life expectancy[2], persisting disability and reduced quality of life[3], and high medical and societal costs.[4]

Joint inflammation in RA is treated by methotrexate and other conventional Disease-Modifying Anti-Rheumatic Drugs (DMARDs). If methotrexate proves insufficient more intensive treatments are used, including combinations of conventional DMARDs[5]

(previously demonstrated as likely to be cost-effective compared with DMARD monotherapy),[6] and biologic drugs like Tumour Necrosis Factor inhibitors (TNFis). Both approaches are clinically effective. While biologics show promise of cost-effectiveness as part of a treatment escalation approach,[7] they are nevertheless substantially more expensive and carry ongoing cost-effectiveness[8] and affordability concerns; methodological nuances also add to uncertainty over their cost-effectiveness.[8]

In the TACIT trial, we compared clinical and economic outcomes of two intensive treatment strategies in patients with active RA who have failed to respond to methotrexate and another DMARD. One strategy was based on initially using combinations of conventional DMARDs (cDMARDs), using biologics only if patients failed to respond after 6 months. The other strategy was based on starting biologic therapy with tumour necrosis factor inhibitors (TNFis). Clinical outcomes showed starting with combinations of cDMARDs gave non-inferior clinical outcomes to starting with TNFis[9]. We now report the associated pre-planned economic evaluation.

MATERIALS AND METHODS

Design and Intervention

The TACIT trial was an open-label, 12-month, pragmatic, randomised, multicentre, two-arm, non-inferiority trial comparing two treatment strategies for RA patients - one starting with cDMARDS, the other with TNFis.[9] Recruitment started on 1 April 2007 and ended 31 March 2010. University College London Hospital research ethics committee approved the

trial (MREC Reference 07/Q0505/57) and participants provided informed consent. We recruited from 24 rheumatology clinics in England and Wales. We included men and women aged over 18 with disease durations over 12 months who met the 1987 criteria for classification of rheumatoid arthritis and National Institute for Health and Care Excellence (NICE) criteria for starting biologics in England and Wales.[10] (Subsequent to our trial, NICE has recommended that biologics are used only if disease is severe and has not responded to intensive therapy with a combination of cDMARDs).[11] We excluded those unable or unwilling to give informed consent, had not had successful results with or had contraindications to all combinations of disease modifying drugs (including possible pregnancy), had contraindications to TNFis, had serious inter-current illness, or were taking high dose corticosteroids (>10 mg prednisolone). Safety monitoring followed national guidance. Before randomisation all patients had received two disease modifying drugs; 62 had received three; 77 were taking combinations of two or more disease modifying drugs; and 24 were taking prednisone (mean dose 4 mg/day; range 1-7 mg). One hundred and sixty-two patients were receiving methotrexate at baseline (132 oral, 30 subcutaneous); the average dose was 18mg/week (range 5-25mg). Clinical characteristics of the sample, including use of medications, are reported in related publications [9, 12].

The sample size was based on testing the null hypothesis of a difference of >0.22 (minimal clinically important change) on the Health Assessment Questionnaire between the two treatments. With a (one sided) testing level of 5%, we needed a sample size of 176 to achieve 90% power. We recruited 214 patients to allow for non-receipt of treatment or drop-outs. After screening for eligibility, consenting patients were randomised in blocks of

four with allocation stratified by region. MedSciNet generated the allocation sequence; trial staff had no prior knowledge of the allocation sequence.

Patients allocated to the TNFi arm were given a particular TNFi depending on patient preference and local circumstances. Methotrexate was also given to patients on TNFis to maximise efficacy and reduce formation of antichimeric antibodies where necessary. Patients intolerant to methotrexate took another DMARD. TNFi patients had their TNFi stopped and another started for 3 reasons: poor response (Disease Activity Score reduction <1.2) at 3 or 6 months; adverse events from medication; or patient choice. Patients who failed two TNFis, and were not able to start a third, were offered a cDMARD.

Patients allocated to the cDMARDs arm were given cDMARDs with proven efficacy over DMARD monotherapy. These included: triple therapy with methotrexate (methotrexate–sulfasalazine–hydroxychloroquine); other methotrexate combinations (methotrexate–ciclosporin, methotrexate–leflunomide and methotrexate–gold); and a sulfasalazine combination (sulfasalazine–leflunomide). Additional monthly steroids (intramuscular Depo-Medrone (120 mg stat) or equivalent) were used if needed. cDMARDS were stopped for the same three reasons stated above for TNFis but poor response was judged at 6 months only. Patients with poor response at 6 months were offered TNFis.

Resource use data

Trial medication use (name, dose, frequency and duration of use) was recorded prospectively on trial proformas by clinical and research staff over the entire study period. Other individual-level economic data were captured by self-report using an adapted Client Service Receipt Inventory (CSRI;[13] see Hurley et al.[14] and Patel et al.[15] for similar applications), by interviewer-completed survey at baseline, and 6 and 12 months post randomisation, covering the previous 3-months. This covered socio-demographic data; use of (all-cause) community and secondary-based health and social care services and other medications; lost pay from illness-related time off work; receipt of social security benefits.

Costs

Individual-level resource-use data, including trial medications, were multiplied by appropriate unit costs (supplementary appendices 1 and 2) to calculate a cost per participant. Using a detailed approach, medication unit costs were converted into cost per milligram (mg) based on the most cost-efficient pack size, choosing maintenance prices over initial treatment prices and generic prices over branded ones to obtain conservative estimates (supplementary appendix 2). Total costs were then computed at baseline, 6 months and 12 months from three perspectives: health and social care perspective; societal, additionally including participant lost pay due to work absence; and a second societal, which further added social security benefits.

Trial medication costs were available for the full 0-6 and 7-12 month periods; all other costs represented data collection periods of 4-6 months and 10-12 months inclusive, so were doubled to represent 6-month periods. All costs are reported in English pounds sterling at 2010/11 prices and can be converted to United States dollars ($) or Euros using the rates £1 = 1.42 or £1 = 1.28 respectively (based on 2011 purchasing power parities which equalise the purchasing power of the currencies [16]). Discounting was unnecessary.

Outcomes

Cost-effectiveness analyses were based on the trial's primary outcome measure, the Health Assessment Questionnaire (HAQ),[17] accounting for lower scores indicating better outcome. Cost-utility analyses were based on quality-adjusted life years (QALYs), estimated by applying appropriate general population utility weights (Brazier et al.[18]; Dolan et al.[19] to individual health statement measurements using both the Short-Form 36 (SF-36[20]) and the EuroQoL 5-Dimension measure (EQ-5D-3L[21] administered at baseline, 6 and 12 months. QALY gains between baseline and 6 months, and between 6 months and 12 months were then calculated as the total area under the curve.

Analyses

Costs and outcomes were compared at 6 and 12 months and are presented as means and standard deviations. Mean differences between trial arms and 95% confidence intervals (CIs) were obtained using non-parametric bootstrap regressions (1000 repetitions). For cost comparisons, we included covariates for baseline cost from the same cost perspective,

baseline HAQ score, duration of illness, age, sex, region (a stratification factor in the randomisation process) and ethnicity. Outcome comparisons included covariates for baseline values of the same outcome plus baseline HAQ score, duration of illness, age, sex, region and ethnicity.

An electronic data capture system (MedSciNet AB, Stockholm, Sweden; http://medscinet.com) was programmed to disallow individual-item non-response on the service use section of the CSRI. For non-trial medication and other societal impacts, we imputed missing values as necessary (supplementary appendix 3).

We used available cases for each analysis. To explore the potential impact of excluding non-responders we examined socio-demographic and clinical characteristics of responders versus the full sample and, in a sensitivity analysis, imputed missing 6- and 12-month total costs and outcomes using the multiple imputation command in Stata version 11.2.[22] Missing costs were imputed based on variables expected to predict total follow-up costs: baseline HAQ score, duration of illness, age, sex, region, ethnicity, trial arm and equivalent baseline cost (and equivalent cost at 6 months for 12-month imputations). Imputations of follow-up HAQ scores were based on baseline HAQ score, duration of illness, age, sex, region, ethnicity and trial arm (and HAQ score at 6 months for 12-month imputations). Imputations of missing QALYs were based on baseline HAQ score, duration of illness, age, sex, region, ethnicity, trial arm and equivalent baseline utility score (and utility score at 6

months for 12-month imputations). Resulting full sample cost and outcome data were analysed as per the main analyses.

Cost-effectiveness and cost-utility analyses

Accounting for the three cost perspectives and three outcomes, there were nine possible cost-outcome combinations to consider in the economic evaluation. Incremental cost-effectiveness ratios (ICERs) were calculated only for combinations showing both significantly higher costs and better outcomes in either trial arm.

Uncertainty around cost-effectiveness/cost-utility from a health and social care perspective was explored using cost-effectiveness acceptability curves (CEACs) based on the net-benefit approach[23] to present the probability that the cDMARDS arm is cost-effective compared with the TNFis arm for a range of values (from £0 and £50,000) that a decision-maker would be willing to pay for an additional QALY or an additional point improvement in HAQ score.

Data were analysed using Stata version 11.2.[22]

Trial registration

ISRCTN (International Standard Registered Clinical/soCial sTudy Number) 37438295

RESULTS

Response rates

Two-hundred and five participants were recruited into the study: 101 into the TNFis arm and 104 into the cDMARDs arm. Details of trial medications are reported in related publications [9, 12]. Response rates to CSRI and outcome questionnaires and completion of trial medication data were 90% or above for all components at baseline and 6 and 12 months and across both trial arms. 191 (93%) participants had both cost and outcome data at 6 month follow-up and 186 to 188 (91 to 92%) had both cost and outcome data at 12 month follow-up. There were no notable differences in characteristics between the subsamples included in the available case analyses and the full sample (Table 1).

Resource use

Resource use (not tested statistically) was broadly comparable between groups (Table 2). General practitioner (GP) surgery visits, practice nurse surgery visits, repeat prescription requests and hospital outpatient appointments were common in both groups at all-time points, with other service use being relatively rare. The number of participants using non-trial concomitant medications was also similar in both groups at all-time points.

Costs

Costs for both groups were equivalent at baseline (Table 3). Costs of social security benefits and lost income are small relative to health and social care costs. At 6 and 12 month follow-

up, average values for cost categories remained equivalent between groups except for cost of trial medications, which was significantly lower in the cDMARDs arm (6-month adjusted mean difference −£3637, 95% CI −£3838 to −£3420; 12-month adjusted mean difference −£1894, 95% CI −£2320 to −£1427). The additional trial medication cost in the TNFis group overshadowed all other cost categories in that arm. The increase in trial medication costs between 6 and 12 months in the cDMARDs arm was due to a significant proportion of this group (n=46; 44%) switching to the more expensive TNFis at 6 months because of non-response to cDMARDs by 6 months. Switching in the reverse direction was uncommon (a total of four participants), so trial medication costs in the TNFis arm did not fall a great deal between 6 and 12 months.

The cDMARDs arm had significantly lower total costs from all perspectives at both follow-ups. The difference is greater at 6 months than at 12 months because of the greater trial medication cost differential before switching taking place. Costs from both societal perspectives are similar to those from a health and social care perspective because of the dominance of trial medication costs.

Outcomes

At baseline, the cDMARDs arm had an advantage on utility scores estimated from the SF-36 but this did not carry through as an advantage in (baseline-adjusted) utility scores at either of the follow-ups or in the resulting QALY estimates (Table 4). The cDMARDs arm did,

however, show advantages in terms of the HAQ and EQ-5D-3L based utility scores at 12 months, although the latter did not translate into QALY advantages.

Cost-effectiveness and cost-utility

Based on the HAQ, the cDMARDs arm dominated with better outcomes and lower costs at 12 months from all three perspectives. All other cost-outcome combinations similarly suggested that the cDMARDs strategy was preferable given equivalent outcomes were achieved at a significantly lower cost. CEACs showed high probabilities of cost-effectiveness for all examined cost-outcome combinations (Figure 1). Probabilities of cost-effectiveness at 6 months based on the HAQ were noticeably reduced after reaching thresholds greater than £10,000 per point improvement, but were consistently high at 12 months. Sensitivity analyses based on imputed missing data produced the same conclusions.

DISCUSSION

Key Findings

We show that, for patients with active RA who have failed to respond to methotrexate and another DMARD, starting treatment with cDMARDs produces similar HAQ and QALY outcomes at 6 months compared to starting treatment with TNFis, and is significantly cheaper (from all cost perspectives) largely due to the lower costs of cDMARD medications compared with TNFis. By 12 months, the cDMARD strategy has the advantage of statistically

significant better HAQ outcomes (−0.16, 95% CI −0.32 to −0.01) although the cost difference is smaller due to the large proportion (44%) of people switching from cDMARDs to TNFis. The HAQ improvement is not clinically significant, so the clinically relevant conclusion is that the cDMARDs strategy provides non-inferior clinical outcomes to the TNFis strategy, but at significantly lower cost to the health and social care system. Adverse events are fully described elsewhere [9] but it is worth noting that serious adverse events and withdrawals because of toxicity were equally common with cDMARDs and TNFis. The total number of adverse events (ranging serious to minor) was though higher with cDMARDs, mainly due to 88 more adverse events related to the digestive system (148 vs. 60) and 20 more adverse events related to the nervous system (61 vs. 41).

Strengths and Limitations

This was a comprehensive and prospective economic evaluation, embedded within a robustly designed and implemented clinical trial with high follow-up rates. Other trials of cDMARDs have lacked such broad perspectives (e.g. Wailoo et al.[24]). The multi-centre design and broad cost perspective necessitated some self-report, risking recall bias; we mitigated such risk by restricting recall periods to 3 months but this then necessitated data extrapolation to generate data for a 6-month period, which may not accurately reflect any variations in service use and other economic impacts across the measured and non-measured periods. Nevertheless, such biases are likely to be equivalent between arms and minimal given our finding that trial medication costs dominated total costs - these more influential medication data were available for the entire follow-up and were recorded prospectively by clinicians and the research team. Finally, we were unable to include

informal care costs and only report one-year outcomes as longer-term modelling was beyond the scope of this study.

Comparison with other studies

There is now extensive evidence that intensive treatment strategies involving conventional DMARDs and, to an extent, glucocorticoids, are cost-effective as well as beneficial in early RA [6,24,25]. In early RA, economic analyses from all three published head-to-head trials comparing cDMARD combinations with TNF inhibitors with methotrexate show biologic strategies are not cost-effective by conventional standards and that DMARDs are preferred. [26,27,28] For example, Eriksson et al.'s [27] examination of infliximab (TNFi) against conventional combination treatment reached similar conclusions of greater costs and lack of cost-effectiveness for the TNFi in a comparable trial-based economic evaluation covering 21 months. The only other head-to-head trial in established RA (RACAT Trial[29]) similarly concludes as us that initiating biologics before triple therapy (combination cDMARDs) is not cost-effective. Using modelling, Stevenson et al. [30] argue that, in England, the cost-effectiveness of biologics for RA is questionable and will only be economically worthwhile in those with the worst prognoses.

The BeSt trial demonstrated that biologics might be cost-effective when accounting for lost productivity.[28] The DRESS trial concluded that optimising TNFi dosing - to titrate to lowest dose - offers substantial cost savings without clinically significant QALY detriments.[31]

More commonly, modelling-, rather than trial-, based studies have been used to justify the higher treatment cost of TNFis and other biologics by showing prevention of, or slowed, RA progression over longer time horizons. For example, Stephens et al. [32] examined combination adalimumab (TNFi) plus methotrexate (DMARD) versus methotrexate alone for people with early aggressive RA in a 30-year simulation based on data from a short-term clinical trial (PREMIER), concluding cost savings and thus cost-effectiveness when accounting for irreversible radiographic damage and lost productivity costs.

However, recent reviews [33,34] highlight contradictory findings, methodological nuances and/or moderate to high cost-effectiveness ratios for biologics. For example, Joensuu et al.'s [34] systematic review (with quality assessment) of 41 cost-utility analyses included 21 studies comparing biologics and cDMARDs in patients with insufficient response to cDMARDs. While incremental cost-effectiveness ratios appeared unrelated to study quality, they naturally varied by specific study features (e.g. sub-group, specific medications and comparators) or were contradictory. Against current cost-effectiveness thresholds, results broadly suggested that biologics lacked cost-effectiveness in treatment naive patients and patients with inadequate responsive to DMARDs. However, at higher thresholds of 50,000–100,000 Euros/QALY, biologics might be cost-effective among cDMARD resistant patients. Of note, all except three of the studies reviewed by Joensuu et al. [34] were modelling studies (using multiple data sources including trials and registries).

Modelling approaches are helpful when pursued with care [35,36] but can carry challenges and limitations. For example, Heather et al. [37] found that only one fifth of model-based economic evaluations of TNFis they reviewed accounted for adverse drug event costs (and not always with transparency on how this was done) which may bias cost-effectiveness estimates for TNFis. Trials that assess a range of resource use inherently include such effects if the follow up period is of sufficient duration, as is the case here. Further, Tosh et al.'s [38] review of how RA treatment sequencing has been modelled suggested weaknesses in underlying evidence and in methods reporting, again generating cost-effectiveness uncertainty. Treatment decisions for people with RA can be complex, in practice and for modelling.[39] Tran-Duy et al. [39] used observational data to inform a simulation of long term outcomes and cost-effectiveness of (a Dutch clinical guideline-informed) treatment strategy where both DMARDs and biological response modifiers (BRMs) are available against a strategy without BRMs. They suggested their flexible modelling approach could helpfully incorporate factors that determine disease progression, costs and outcomes, although their simulated ICER for the strategy including BRMs exceeded conventional thresholds for cost-effectiveness.

There is thus a mixed picture of cost-effectiveness for RA treatment. Models remain reliant on high quality trial-based or observational evidence to underpin estimates of short-term treatment response; our high quality trial can usefully inform future such studies. There remains uncertainty about the relative cost-effectiveness of different drugs within each class due to a paucity of head to head comparisons.[40,41,42] Treatments also continue to evolve. Substantially cheaper biosimilars are now becoming available; these can drive down

the costs of original drugs and modelling studies in countries where they have been used suggest they will improve the cost-effectiveness of these treatments,[43] though the way this will impact upon the routine clinical use of biologics in RA is not yet fully known.

CONCLUSION

This economic evaluation suggests that for patients with established RA who have failed to respond to methotrexate and another DMARD, beginning treatment with cDMARDs is a more cost-effective treatment approach, since it provides equivalent outcomes to starting treatment with TNFis and either avoids or delays additional costs associated with the more expensive TNFis. This offers a pragmatic response to financial challenges presented by new and more expensive treatments.

REFERENCES

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010;376:1094–108.

2. Sokka T, Abelson B, & Pincus T. Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol*, 2008;26(Suppl.51):S35–61.

3. Scott DL & Steer S. The course of established rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007;21:943–67.

4. Pugner KM, Scott D, Holmes JW, Hieke K. The costs of rheumatoid arthritis: an international long-term view. *Semin Arthritis Rheum* 2000;29:305–20.

5. Bakker MF, Jacobs JWG, Verstappen SMM, Bijlsma JWJ. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. *Ann Rheum Dis* 2007;66(SupplIII):iii56–iii60.

6. Tosh JC, Wailoo AJ, Scott DL, Deighton CM. Cost-effectiveness of combination nonbiologic disease-modifying antirheumatic drug strategies in patients with early rheumatoid arthritis. *J Rheumatol* 2011;38(8):1593-600.

7. Schoels M, Wong J, Scott DL, Zink A, Richards P, Landewé R, et al. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;69(6):995-1003.

8. Losina E, Katz JN. Improvement at any cost? The art and science of choosing treatment strategies for rheumatoid arthritis. *Ann Intern Med* 2017 2017;167(1):55-56.

9. Scott DL, Ibrahim F, Farewell V, O'Keeffe AG, Walker D, Kelly C, et al. Tumour necrosis factor inhibitors versus combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT non-inferiority randomised controlled trial. *BMJ* 2015;350:h1046

10. National Institute for Health and Care Excellence (2007). Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 130).

11. National Institute for Health and Care Excellence (2016). Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (NICE technology appraisal guidance 375). Available at: https://www.nice.org.uk/guidance/ta375 (Accessed 3 July 2017).

12. Scott DL, Ibrahim F, Farewell V, O'Keeffe AG, Ma M, Walker D, Heslin M, Patel A, Kingsley G. Randomised controlled trial of Tumour necrosis factor inhibitors Against Combination Intensive Therapy with conventional disease-modifying antirheumatic drugs in established rheumatoid arthritis: the TACIT trial and associated systematic reviews. *Health Tech Assess* 2014; 18 (66): 1-192.

13. Beecham, Knapp M. Costing psychiatric interventions. In Thornicroft G, Brewin C, Wing JK, eds. Measuring Mental Health Needs. London: Gaskell; 1992: 203–27.

14. Hurley MV, Walsh NE, Mitchell H, Nicholas J, Patel A. Long-term outcomes and costs of an integrated rehabilitation program for chronic knee pain: a pragmatic, cluster randomized, controlled trial. *Arthritis Care Res* 2012;64:238–47.

15. Patel A, Buszewicz M, Beecham J, Rait G, Nazareth I, Atkinson A, et al. Economic evaluation of arthritis self management in primary care. *BMJ* 2009;339:b3532.

16. OECD. Stat. National Accounts, Table 4: PPPs and exchange rates. At: http://stats.oecd.org/Index.aspx?DataSetCode=SNA_TABLE4 (Accessed 23 September 2018).

17. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-45.

18. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21:271–92.

19. Dolan P, Gudex C, Kind P, Williams A. A Social Tariff for EuroQol: Results from a UK Population Survey. York: University of York; 1995.

20. Ware J, Sherbourn C. The MOS, 36 item short-form health survey (SF-36). I: conceptual framework and item selection. *Med Care* 1992;30:473-83.

21. EuroQol Group. EuroQol: a facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.

22. StataCorp (2009). Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.

23. Briggs AH. A Bayesian approach to stochastic cost-effectiveness analysis. *Health Econ* 1999;8:257–61.

24. Wailoo A, Hernández Alava M, Ibrahim F, Scott DL. Cost-effectiveness of treatment strategies using combination disease-modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis. *Rheumatology* 2014;53(10):1773-7.

25. de Jong PH, Hazes JM, Buisman LR, Barendregt PJ, van Zeben D, van der Lubbe PA, et al. Best cost-effectiveness and worker productivity with initial triple DMARD therapy compared with methotrexate monotherapy in early rheumatoid arthritis: cost-utility analysis of the tREACH trial. *Rheumatology* 2016;55:2138-2147.

26. Jalal H, O'Dell JR, Bridges SL Jr, Cofield S, Curtis JR, Mikuls TR, et al. Cost-effectiveness of triple therapy versus Etanercept plus Methotrexate in early aggressive rheumatoid arthritis. *Arthritis Care Res* 2016;68:1751-1757.

27. Eriksson JK, Karlsson JA, Bratt J, Petersson IF, van Vollenhoven RF, Ernestam S, et al. Cost-effectiveness of infliximab versus conventional combination treatment in methotrexate-refractory early rheumatoid arthritis: 2-year results of the register-enriched randomised controlled SWEFOT trial. *Ann Rheum Dis* 2015;74(6):1094-101.

28. van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, de Vries-Bouwstra JK, Hazes JM, Kerstens PJ, et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. *Arthritis Rheum* 2009;61:291-9.

29. Bansback N, Phibbs CS, Sun H, O'Dell JR, Brophy M, Keystone EC, et al. Triple therapy versus biologic therapy for active rheumatoid arthritis: a cost-effectiveness analysis. *Ann Intern Med* 2017; 167(1):8-16.

30. Stevenson MD, Wailoo AJ, Tosh JC, Hernandez-Alava M, Gibson LA, Stevens JW, et al. The cost-effectiveness of sequences of biological disease-modifying antirheumatic drug treatment in England for patients with rheumatoid arthritis who can tolerate methotrexate. *J Rheumatol* 2017; 44(7):973-980.

31. Kievit W, van Herwaarden N, van den Hoogen FH, van Vollenhoven RF, Bijlsma JW, van den Bemt BJ, et al. Disease activity-guided dose optimisation of adalimumab and etanercept is a cost-effective strategy compared with non-tapering tight control rheumatoid arthritis care: analyses of the DRESS study. *Ann Rheum Dis* 2016;75(11):1939-1944.

32. Stephens S, Botteman MF, Cifaldi MA, van Hout BA. Modelling the cost-effectiveness of combination therapy for early, rapidly progressing rheumatoid arthritis by simulating the reversible and irreversible effects of the disease. *BMJ Open* 2015;5(6):e006560.

33. van der velde G, Machado M, Ieraci L, Ieraci L, Witteman W, Bombardier C, et al. Cost-effectiveness of biologic response modifiers compared to disease-modifying antirheumatic drugs for rheumatoid arthritis: a systematic review. *Arthritis Care Res* 2011;63(1):65–78.

34. Joensuu JT, Huoponen S, Aaltonen KJ, Konttinen YT, Nordström D, Blom M. The cost-effectiveness of biologics for the treatment of rheumatoid arthritis: a systematic review. *PLoS One* 2015;10(3):e0119683.

35. Marra CA, Bansback N, Anis AH, Shojania K. Introduction to economic modelling for clinical rheumatologists: application to biologic agents in rheumatoid arthritis. *Clin Rheumatol* 2011; 30(Suppl.1):S9–18.

36. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting

the appropriate approach. *J Health Serv Res Policy* 2004;9:110–18.

37. Heather EM, Payne K, Harrison M, Symmons DP. Including adverse drug events in economic evaluations of anti-tumour necrosis factor-α drugs for adult rheumatoid arthritis: a systematic review of economic decision analytic models. *Pharmacoeconomics* 2014 32(2):109-34.

38. Tosh J, Stevenson M, Akehurst R. Health economic modelling of treatment sequences for rheumatoid arthritis: a systematic review. *Curr Rheumatol* Rep 2014;16(10):447.

39. Tran-Duy A, Boonen A, Kievit W, van Riel PL, van de Laar MA, Severens JL. Modelling outcomes of complex treatment strategies following a clinical guideline for treatment decisions in patients with rheumatoid arthritis. *Pharmacoeconomics* 2014;32(10):1015-28.

40. Turkstra E, Ng SK, Scuffham PA. A mixed treatment comparison of the short-term efficacy of biologic disease modifying anti-rheumatic drugs in established rheumatoid arthritis. *Curr Med Res Opin* 2011;27(10):1885-97.

401. Nguyen CM, Bounthavong M, Mendes MA, Christopher ML, Tran JN, Kazerooni R, et al. Cost utility of tumour necrosis factor-α inhibitors for rheumatoid arthritis: an application of Bayesian methods for evidence synthesis in a Markov model. *Pharmacoeconomics* 2012;30(7):575-93.

42. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(14):1-278.

43. Park SK, Park SH, Lee MY, Park JH, Jeong JH, Lee EK. Cost-effectiveness analysis of treatment sequence initiating with etanercept compared with leflunomide in rheumatoid

arthritis: impact of reduced etanercept cost with patent expiration in South Korea. *Clin Ther* 2016;38:2430-2446.

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Table 1: Characteristics of full sample and sub-sample with costs and HAQ, EQ-5D-3L and SF-36

	Full sample		**Sub-sample with 6month cost and HAQ / EQ-5D-3L / SF-36 data**		**Sub-sample with 12 month cost and EQ-5D-3L data**		**Sub-sample with 12 month cost and HAQ / SF-36 data**	
	(n=205)		***(n=191)***		***(n=186)***		***(n=188)***	
	n	*%*	*N*	*%*	*N*	*%*	*n*	*%*
Gender:								
Male	53	26	45	24	45	24	46	25
Female	152	74	146	76	141	76	142	76
Ethnicity:								
White	181	88	168	88	162	87	164	87
Other	24	12	23	12	24	13	24	13
Region:								
London & South	128	62	127	67	121	65	121	64
Midlands	16	8	13	7	11	6	13	7
North	61	30	51	27	54	29	54	29
	Mean	***Standard deviation***	***Mean***	***Standard deviation***	***Mean***	***Standard deviation***	***Mean***	***Standard deviation***
Age	57.34	11.97	57.11	11.94	56.84	12.08	56.91	12.02
Duration of illness in years	8.20	8.82	8.35	8.98	8.25	8.92	8.24	8.88
HAQ at baseline	1.85	0.63	1.86	0.63	1.85	0.64	1.85	0.64
EQ-5D-3L based utility at baseline	0.37	0.31	0.37	0.31	0.37	0.31	-	-
SF-36 based utility at baseline	0.54	0.11	0.54	0.11	-	-	0.54	0.11

Table 2: Resource use at 6 and 12 month follow-up (for the previous 3 months)

		6 months						12 months					
		TNF (n=97)			DMARDS (n=94)			TNF (n=93)			DMARDS (n=95)		
	Unit	*Number of users*	*Mean**	*SD*	*Number of users*	*Mean**	*SD*	*Number of users*	*Mean**	*SD*	*Number of users*	*Mean**	*SD*
GP													
At surgery	Visit	55	2	1	42	2	1	58	2	2	60	2	1
At home	Visit	3	2	1	2	1	<1	3	1	1	4	2	1
Phone call	Call	14	1	1	9	2	1	13	1	1	16	1	1
Repeat prescription request without GP contact	Prescription	70	3	1	63	3	1	61	2	1	68	3	2
Nurse													
At surgery	Visit	31	3	4	31	3	3	31	2	2	24	2	1
Phone call	Call	2	1	<1	2	2	1	5	2	1	2	1	<1
Physiotherapist													
At hospital	therapy unit	4	3	1	8	4	3	7	3	2	11	5	6
At home	Visit	0	-	-	0	-	-	0	-	-	0	-	-
At GP surgery	Visit	1	1	-	2	3	<1	2	3	3	1	8	-
Elsewhere	Visit	2	2	1	0	-	-	1	2	-	1	1	-
Occupational therapist													
At hospital	therapy unit	3	1	1	4	2	1	1	1	-	6	2	1
At home	Visit	4	1	<1	2	1	<1	1	1	-	1	1	-
At GP surgery	Visit	0	-	-	0	-	-	0	-	-	0	-	-
Elsewhere	Visit	0	-	-	1	1	-	1	3	-	1	1	-
Hospital services													

A&E	Visit	9	1	<1	4	1	<1	5	1	1	10	1	<1
Hospital stay	Night	5	7	5	4	4	5	2	11	13	5	2	1
Outpatient	appointment	58	3	1	55	3	2	55	3	2	56	2	1
Social services													
Meals on wheels	Meal	0	-	-	1	60	-	0	-	-	0	-	-
Home help	Visit	2	46	63	1	1	-	3	31	51	0	-	-
Social worker	Hour	3	1	1	3	1	1	2	2	<1	1	1	-
Social worker phone call	contact	1	3	-	1	2	-	1	1	-	2	2	1
Other health or social service	service	3	14	11	3	31	51	2	1	<1	2	19	16
Non-trial medication	n/a	94	-	-	88	-	-	91	-	-	90	-	-

*Mean for users only

Table 3: Summary costs at baseline, 6 and 12 months (for the previous 3 months)

	TNF n=101			DMARDs n=104			Unadjusted mean difference[$]	95% C.I.[$]	Adjusted mean difference[$$]	95% C.I.[$$]
	valid n	*Mean £*	*SD*	*valid n*	*Mean £*	*SD*				
Costs at baseline (previous 3 months)										
Health & social care, excluding trial medication**	101	736	1082	104	601	476	-131	-379 to 97	-	-
Lost pay**	101	60	262	104	84	440	24	-66 to 131	-	-
Social security benefits**	101	71	76	104	63	67	-9	-29 to 12	-	-
Costs at 6 months (previous 3 months)										
Health & social care, excluding trial medication**	97	536	947	94	511	705	-27	-262 to 202	6	-217 to 206
Lost pay**	97	71	405	94	35	310	-35	-127 to 67	-35	-115 to 59
Social security benefits**	97	77	75	94	74	77	-2	-21 to 21	3	-15 to 19
Trial medication costs***	97	4166	1012	97	510	356	-3660*	-3855 to -3432	-3637*	-3838 to -3420
Costs at 12 months (previous 3 months)										
Health & social care, excluding trial medication**	95	659	1699	93	583	634	-74	-486 to 255	-24	-363 to 230
Lost pay**	93	19	132	95	2	18	-16	-46 to 2	-17	-42 to 2
Social security benefits**	93	85	83	95	77	84	-6	-32 to 16	5	-12 to 23
Trial medication***	96	3546	1631	94	1547	1547	-1988*	-2458 to -1555	-1894*	-2320 to -1427
Total costs extrapolated to 6 months										
Costs at 6 months (previous 6 months										
Health & social care perspective, including trial medication	97	5238	2093	94	1538	1393	-3703*	-4175 to -3199	-3615*	-4104 to -3182

Societal perspective, including trial medication, excluding social security benefits	97	5379	2236	94	1607	1569	-3774*	-4298 to -3230	-3683*	-4198 to -3195
Societal perspective, including trial medication, including social security benefits	97	5533	2241	94	1755	1591	-3778*	-4303to -3230	-3684*	-4199 to -3194
Costs at 12 months (previous 6 months)										
Health & social care, including trial medication	93	4866	3147	95	2718	1890	-2129*	-2941 to -1417	-1930*	-2599 to -1301
Societal, including trial medication, excluding social security benefits	93	4904	3218	95	2722	1890	-2162*	-2977 to -1449	-1974*	-2648 to -1334
Societal, including trial medication, including social security benefits	93	5073	3208	95	2876	1914	-2175*	-2991 to -1465	-1977*	-2644 to -1338

[$]Comparisons include a covariate for region

[$$]Comparisons include covariates for equivalent baseline cost, baseline HAQ, duration of illness, age, gender, region and ethnicity

* Statistically significant

** 3-month costs

*** 6-month costs

Table 4: HAQ and QALY outcomes at baseline, 6 and 12 months

	TNF			DMARDs			Unadjusted mean difference[$]	95% C.I.	Adjusted mean difference[$$]	95% C.I.[$]
	valid n	*Mean*	*SD*	*valid n*	*Mean*	*SD*				
Utilities and HAQ										
Baseline										
SF-36 utility	101	0.52	0.11	104	0.56	0.10	0.04	0.01 to 0.07	-	-
EQ-5D-3L utility	101	0.35	0.31	104	0.39	0.31	0.04	-0.04 to 0.12	-	-
HAQ	101	1.90	0.67	104	1.80	0.59	-0.10	-0.28 to 0.07	-	-
6 months										
SF-36 utility	97	0.59	0.13	94	0.62	0.12	0.03	-0.01 to 0.06	0.00	-0.03 to 0.03
EQ-5D-3L utility	97	0.53	0.30	94	0.56	0.26	0.03	-0.05 to 0.10	-0.01	-0.08 to 0.06
HAQ	97	1.55	0.83	94	1.52	0.65	-0.03	-0.22 to 0.19	0.07	-0.08 to 0.21
12 months										
SF-36 utility	94	0.60	0.14	94	0.64	0.13	0.04	0.01 to 0.08	0.03	-0.00 to 0.07
EQ-5D-3L utility	93	0.50	0.31	94	0.60	0.28	0.10	0.02 to 0.19	0.10	0.02 to 0.18*
HAQ	94	1.60	0.84	95	1.33	0.77	-0.27	-0.51 to -0.04	-0.16	-0.32 to -0.01*
QALYs										
6 months										
SF-36 QALYs	97	0.28	0.05	94	0.30	0.05	0.02	0.00 to 0.03	0.00	-0.01 to 0.01
EQ-5D-3L QALYs	97	0.22	0.14	94	0.24	0.12	0.02	-0.02 to 0.05	0.00	-0.02 to 0.02

12 months										
SF-36 QALYs	93	0.30	0.06	87	0.32	0.05	0.02	-0.00 to 0.03	0.01	-0.00 to 0.02
EQ-5D-3L QALYs	92	0.26	0.13	88	0.29	0.11	0.03	-0.01 to 0.06	0.02	-0.01 to 0.05

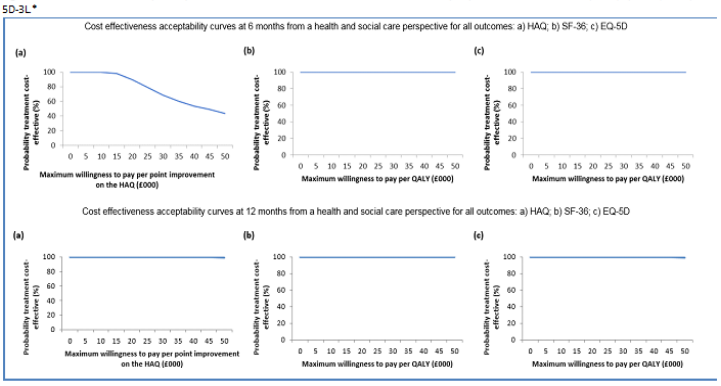
[$]Comparisons include a covariate for region

[$]Comparisons of HAQ include covariates for baseline HAQ, duration of illness, age, gender, region and ethnicity; comparisons of utilities and QALYs include covariates for appropriate baseline utility, baseline HAQ, duration of illness, age, gender, region and ethnicity

*Statistically significant

Figure 1: Cost-effectiveness acceptability curves at 6 and 12 months from a health and social care perspective for all outcomes: a) HAQ; b) SF-36; and c) EQ-5D-3L.*

Figure 1: Cost-effectiveness acceptability curves at 6 and 12 months from a health and social care perspective for all outcomes: a) HAQ; b) SF-36; and c) EQ-5D-3L.*



* Coefficients of differences in net benefits between the trial arms were obtained through a series of bootstrapped linear regressions (1000 repetitions) of group upon net benefit; we included covariates for baseline values of the same cost category, the same outcome, HAQ score, duration of illness, age, sex, region and ethnicity.